

Chemotherapy-induced Anaemia

a report by

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Anaemia is a frequent complication of malignancy and is aggravated by chemotherapy.^{1,2} Up to 90% of cancer patients experience anaemia during the course of the disease;¹ however, the frequency varies with the type and stage of the tumour and treatment. Chemotherapy reduces the haemoglobin (Hgb) level by inducing a suppressive effect on bone marrow and toxic effects on erythrocytes. The incidence of anaemia has been correlated directly with the number of chemotherapy cycles the patient receives.³ Early studies demonstrated a profound adverse impact of anaemia on a cancer patient's functional capacity, quality of life (QOL), prognosis and survival.⁴⁻⁶ Pre-clinical studies have shown that anaemia is associated with antineoplastic therapy resistance,^{7,8} which is partially attributed to the hypoxic effect of anaemia and the reliance of ionising radiation, as well as certain types of chemotherapy agents, on adequate tissue oxygenation for their ability to kill cancer cells. Therefore, anaemia theoretically contributes to furthering malignant progression and tumour survival in the oncology anaemic patients.⁹⁻¹⁴

Treatment of CIA

In malignant patients, it is crucial to consider potential reversible aetiologies of anaemia before starting erythropoiesis-stimulating agents (ESAs). Therefore, a comprehensive history and physical examination are warranted, and the exposure list of the medications should be reviewed. Screening diagnostic tests should be conducted, which include iron studies, folate, vitamin B₁₂ and peripheral blood smear. Patients should be evaluated for occult blood loss and renal insufficiency. In patients with underlying chronic lymphocytic leukaemia and non-Hodgkin's lymphoma, direct Coomb's testing may be needed to exclude an autoimmune mechanism of anaemia. Blood transfusion was the cornerstone therapy for many years in chemotherapy-induced anaemia (CIA), although this trend has changed because ESAs have decreased transfusion requirements. However, transfusion remains the first-line therapy if acute intervention is required and in patients who have failed or have contraindications to ESAs. In addition, the change in US Food and Drug Administration (FDA) indication does not allow ESAs to be given to CIA patients treated with curative intent.

The Introduction of ESAs and Their Efficacy in Reducing Transfusion Requirements

Three different recombinant erythropoietins (Epo) are available: epoetin alfa, pegzerepoetin alpha and darbepoetin alpha. Pegzerepoetin alpha is not commercially available in the US. Darbepoetin alpha has an additional N-linked oligosaccharide chain that provides a three-fold greater terminal half-life with a five-fold lower affinity for Epo receptors compared with erythropoietin alfa.¹⁶ Trials and comprehensive systematic reviews have shown equality of the different ESAs in Hgb rise and a reduction of transfusion requirements or thromboembolic incidence;¹⁷⁻²¹ therefore, the indications, concerns and warnings are similarly applied for all ESAs. Epoetin alfa was approved by the FDA for treating CIA in patients with non-

myeloid malignancies in 1993, followed by darbepoetin alpha in 2002. Trials have established their efficacy in raising Hgb levels and reducing blood transfusion,²²⁻²⁵ and a systematic review by Bohlius et al. has found that treatment with ESAs increases Hgb levels and reduces the need for blood transfusions by 40%, with an average of one unit fewer of red blood cells (RBCs) transfusion in patients receiving ESAs compared with the control group.²⁴ The advantage of ESAs over blood transfusion is their ability to induce a more sustained correction of Hgb, remove the risk of blood-borne infectious agents and confer a more convenient therapy for the patient. The use of ESAs has spread worldwide and has emerged as one of the most utilised medications in oncology, despite the fact that studies have never proved a survival benefit. The rationale behind their spread was the belief of their ability to promote QOL.

Do ESAs Improve QOL in Patients with CIA?

Evaluating the influence of ESAs on QOL is a complex matter. In a Cochrane review in 2008, Epo was associated with a small but significant improvement of QOL in patients with CIA compared with placebo (p=0.008). Darbepoetin alpha also illustrated a small but significant enhancement of QOL compared with placebo (0.05).²⁶ Although studies have reported variable effects of ESAs on patient QOL,²⁷⁻³¹ they do not currently meet the criteria for FDA approval as an indication in CIA.¹⁵ Previously, ESAs were heavily marketed for their QOL-enhancing properties, but now in the US commercials advertising ESAs improvements on QOL in CIA are not allowed.

Side Effects of ESAs

ESAs and the Risk of VTE

ESAs cause an increased incidence of venous thromboembolic events (VTEs) based on randomised trials^{32,33} and systematic reviews.^{24,34-36} A Cochrane meta-analysis in 2006 reported a higher incidence of VTE in patients receiving ESAs in contrast to control groups (relative risk [RR] 1.67, 95% confidence interval [CI] 1.35-2.06);²⁴ a similar outcome was reported by Bennett et al. in a 2008 meta-analysis (RR 1.57, 95% CI 1.31-1.87).³⁵ Therefore, ESAs should not be given at all – or should be given cautiously – to patients at risk of VTE, including patients with immobility, recent surgery and a history of thrombotic events. Patients being treated with some types of chemotherapy increase their risk of thrombosis, such as multiple myeloma regimens, including thalidomide and high-dose dexamethasone.³⁷

Effect of ESAs on Tumour Progression and Overall Survival

The effect of ESAs on tumour control and progression has been questioned since some studies have shown a higher degree of tumour progression in patients receiving ESAs.^{33,38-39} Epo is a growth factor synthesised in the kidneys and released into the plasma in response to tissue hypoxia; it binds to Epo receptors (EpoR) on the surface of RBC precursors located in the bone marrow. However, EpoR has been found to

Table 1: Guidelines for ESAs

	ASH/ASCO ⁵⁹	NCCN ⁵⁷	EORTC ⁵⁸	CMS ⁶⁰	FDA ¹⁵
Hgb threshold to start ESA	Hgb approaching or falls below 10g/dl	Hgb \leq 11g/dl, it can be started if Hgb 11.1–11.9 based on the clinical situation	Hgb \leq 11g/dl, it can be started if Hgb 11.1–11.9 is based on the clinical situation	If Hgb <10g/dl	If Hgb <10g/dl
Target of Hgb	Around 12g/dl	Around 12g/dl	Around 12g/dl	10g/dl	Hgb approaches level that is required to avoid transfusion

ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; EORTC = European Organisation for Research and Treatment of Cancer; CMS = Centers for Medicare & Medicaid Services; FDA = US Food and Drug Administration; Hgb = haemoglobin; ESA = erythropoiesis-stimulating agents.

be expressed in various cancers such as head and neck, breast, lung, colon, gastric and uterine tumours.^{40–45} Theories suggest that ESAs may contribute to stimulating tumour growth and survival through binding EPO and mediating a circuit of signalling pathways.^{46–48}

ESAs in cancer-related anaemia not caused by chemotherapy are associated with an adverse effect on survival. The Epoetin Alfa in Advanced Non-Small Cell Lung Cancer (EPO-CAN-20) trial enrolled patients with metastatic non-small-cell lung cancer and cancer-related anaemia with Hgb <12.1g/dl. Patients were double-blinded and randomised to either epoetin alpha or placebo. The targeted Hgb was 12–14g/dl. The study was suspended early after a superior overall survival (OS) was observed in patients receiving placebo (129 versus 63 days; $p=0.04$).⁴⁹

The Amgen 20010103 study is a phase III randomised, double-blinded trial that included 989 patients with cancer-related anaemia not undergoing active cancer therapy. Enrolled patients had an Hgb level of <11g/dl and the Hgb target was 12–13g/dl. Patients were randomised to receive darbepoetin alpha or placebo. Unfavourable outcome was seen in the darbepoetin alpha group compared with the placebo group, characterised by shorter OS (8 versus 10.8 months) and failure in reducing the need for transfusion.⁵⁰

There is no role for ESAs in cancer patients receiving chemotherapy with a normal Hgb level, as data have shown adverse responses in terms of OS when ESAs are used in non-anaemic patients.³² The Breast Cancer Erythropoietin Survival Trial (BEST) randomised non-anaemic patients with metastatic breast cancer receiving chemotherapy to epoetin alpha or placebo, targeting Hgb levels of 12–14g/dl. The study was terminated prematurely as early analysis demonstrated a trend of declining one-year survival in the epoetin alpha group (70%) compared with the placebo group (76%) ($p=0.012$).³²

In the Danish Head and Neck Cancer Group (DAHANCA) 10 study, 522 patients were randomly assigned to receive radiotherapy plus darbepoetin alpha or radiotherapy alone in head and neck cancer. The target Hgb was 14–15g/dl. The study was terminated early because preliminary analysis demonstrated a significantly decreased five-year locoregional tumour control in the darbepoetin arm compared with the control group (RR 1.44; $p=0.02$). OS was lower in the ESAs group, but did not reach statistical significance (RR 1.28; $p=0.08$).³⁸

The Erythropoietin in Head and Neck Cancer (ENHANCE) trial randomised non-anaemic patients with head and neck cancer receiving radiotherapy to either placebo or pegzerepoetin alpha, aiming for an Hgb level of 14–15g/dl. The pegzerepoetin alpha group had a substantially shorter locoregional progression-free survival (PFS) (hazard ratio [HR] 1.62; $p=0.0008$) and shorter

time to locoregional progression (HR 1.69; $p=0.007$), as well as decreased OS, compared with the placebo group (HR 1.39; $p=0.02$).³³

The Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE) trial randomised 733 patients with breast cancer receiving neoadjuvant chemotherapy to placebo or darbepoetin alfa. Hgb was maintained between 12.5 and 13g/dl. Patients who received ESAs were found to have shorter three-year OS (86 versus 90%) and relapse-free survival rate (72 versus 78%) than those on placebo. Moreover, tumour progression was faster in the patients treated with darbepoetin alfa.⁵¹

In another randomised trial, by the National Cancer Institute (NCI) Gynecologic Oncology Group (GOG), 114 patients with advanced cervical cancer receiving concurrent cisplatin and radiotherapy were randomly assigned to receive ESAs or transfusion when the Hgb concentration was \leq 10mg/dl. The study was terminated early when a data analysis showed lower three-year OS (59 versus 62%) and PFS (61 versus 71%) in patients treated with epoetin alpha compared with the standard of care.³⁹

Despite the uncertain effect of ESA therapy on survival rates that were reported in earlier meta-analyses,²⁴ the result of a more recent large meta-analysis, which was obtained from 51 phase III trials conducted between 1985 and 2008, has established a statistically significant increased mortality in patients receiving ESA therapy (HR 1.10, 95% CI 1.01–1.20; $p=0.03$).³⁵

Iron Supplements with ESAs

Iron status should be assessed and replaced in iron-deficient patients prior to starting ESA therapy. However, cancer patients have a functional iron deficiency as a consequence of inadequate mobilisation of iron from the reticuloendothelial system mediated by cytokines secretion. Several randomised studies have evaluated the benefits of giving iron concurrently with ESA therapy in CIA. Studies compared ESA therapy alone versus ESAs plus oral or intravenous iron supplements during the course of the therapy. Trials have found a favourable effect on haematological response, transfusion requirements and QOL in patients given intravenous (IV) iron rather than oral iron supplement with ESAs compared with ESAs alone.^{52–56}

In a prospective, multicentre study, 157 patients with CIA were randomised to epoetin alpha alone or epoetin alpha with oral iron, iron dextran IV bolus or iron dextran total dose infusion. Mean Hgb concentration increased by 0.9, 1.5, 2.5 and 2.4g/dl, respectively. The difference in the amount of increase of Hgb was statistically significant between patients given IV iron and patients given oral iron or no iron ($p<0.02$), while it was statistically not significant between the epoetin alpha and oral iron versus epoetin alpha alone groups ($p=0.21$).⁵² Parenteral iron appeared to be well tolerated without significant toxicity.

Previous and Current Guidelines for ESAs

ESAs have been approved for treating anaemia in patients with non-myeloid haematological and solid malignancies receiving concurrent myelosuppressive chemotherapy. Although the Hgb threshold that determines the time to initiate ESAs varied slightly between the international guidelines, both the FDA and the Centers for Medicare & Medicaid Services (CMS) have demanded the Hgb level be below 10g/dl before commencing treatment with ESAs.^{15,60} The guidelines from the National Comprehensive Cancer Network (NCCN) 2008⁵⁷ and the European Organization of Research and Treatment of Cancer (EORTC), updated in 2007,⁵⁸ recommended initiating ESAs if the Hgb concentration is ≤ 11 g/dl. On the other hand, the American Society of Hematology and the American Society of Clinical Oncology (ASH/ASCO) 2007⁵⁹ advocate starting ESAs when the Hgb level approaches or has fallen below 10g/dl. However, on 30 July 2008 the FDA revised ESA labelling to require Hgb levels less than 10g/dl before initiating their usage in patients with CIA. It also removed the previous statement regarding the safety of continuing treatment until the Hgb target of 12g/dl is reached and restricted their target by the level that is needed to avoid blood transfusion;¹⁵ however, this new target conflicts with pre-existing international guidelines that set the target around 12g/dl.^{57–59} ESA dosage should be adjusted for each patient to maintain Hgb concentration at the lowest level that is essential to avoid transfusion. Doses should be reduced when an Hgb rise of more than 10g/dl occurs over a two-week period during therapy. Therapy should be stopped if the targeted Hgb is reached, and it can be subsequently resumed with 25% below of the prior dose when Hgb level falls again. The CMS have restricted the coverage of ESAs for patients with cancer who are undergoing chemotherapy. CMS rules demand an Hgb level below 1g/dl for initiating ESAs therapy, and they require discontinuing ESA therapy once the Hgb level of ≥ 10 g/dl is achieved.⁶⁰ ESAs can be continued for two months after the completion of chemotherapy.

The recommended starting dose of epoetin alpha is 150U/kg three times in a week (TIW) or 40,000U weekly subcutaneously. However, the starting dose for darbepoetin alpha is 2.25mcg/kg weekly or 500mcg every three

weeks subcutaneously. The optimal ESA doses have been derived from randomised studies and approved by the FDA.¹⁵

Only around 60% of cancer patients receiving ESA therapy experience an adequate response.⁶¹ Non-response is defined as failure to achieve a rise in Hgb concentration more than 1–2g/dl or a lack in declining transfusion rate within six to eight weeks. ESAs should be stopped in the absence of the appropriate response if the recommended escalated doses have already been attempted. Studies have established the lack of benefits if treatment is continued in these individuals. Non-responders should be investigated for other causes of anaemia apart from chemotherapy and patients should receive a transfusion as necessary. Furthermore, the use of ESAs should be discontinued when the patient's planned chemotherapy course is accomplished or if the therapy is complicated by VTE.

The most recent FDA release prohibited ESA use in patients where chemotherapy is given with curative intent. The FDA has included in a black box warning that studies have shown a negative impact on OS and tumour progression in the following cancers: breast, head and neck, non-small-cell lung, lymphoid and cervical malignancies.¹⁵ The FDA is mandating that all new patients be given a guide detailing the side effects of the ESAs. This guide emphasises that ESAs may increase a patient's risk of death, tumour progression, serious cardiac complications and deep vein thrombosis (DVT). In addition, the sales of ESAs have decreased 14% worldwide and 26% in the US in the last year. Analysts predict that the new labelling will lead to a further 40% decline in sales.⁶³

Conclusion

Due to the effects of ESAs in decreasing OS and increasing tumour progression and the risk of VTE, they are no longer approved for cancer-induced anaemia or cancers in which cure is intended. ESAs are approved by the FDA in CIA to reduce the use of blood transfusions. The FDA guideline in July 2008 mandates Hgb concentration less than 10g/dl prior to starting ESAs in CIA, and doses should be titrated to maintain the lowest Hgb level that is sufficient to avoid transfusion. ■

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